REMARKS

In a Final Office Action dated October 9, 2008, claims 2, 3, 5-7, 9-11, 14-17, 19, and 22-23, all of the claims pending in the above-identified patent application, were rejected. No claim amendments are being made herein. Thus, this paper does not introduce any new matter and its entry is respectfully requested. Applicants respectfully request reconsideration of this application and allowance of the claims.

Withdrawal of Previous Rejection Under 35 U.S.C. §112, second paragraph

The previous rejection of Claims 26-33 under 35 U.S.C. §112, second paragraph, has been withdrawn in view of Applicants' May 21, 2008 amendment.

In response, Applicants acknowledge and appreciate the withdrawal of the rejection.

Claim Rejections Maintained in October 9, 2008 Final Office Action

Claims 2-3, 5-6, 9-11, 14-17, 19, 22-30, and 32-33 remain rejected under 35 USC § 103(a) as allegedly being unpatentable over Geistlich et al. U.S. Patent No. 5,837,278 (Geistlich '278), in view of Stensaas et al. U.S. Patent No. 4,778,467 and further in view of Shimizu U.S. Patent No. 6,090,117. Claims 2-3, 5-7, 9-11, 14-17, 19, and 22-23 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Geistlich, et al. in view of Stensaas et al., in view of Shimizu, and further in view of Humes (U.S. Patent No. 5,429,938). The full rationale for these rejections appears at pages 2-7 of the Office Action.

Specifically, with respect to the first rejection, the Office Action stated that collagen sheet material referred to in the Geistlich '278 patent (i.e., BioGide®) is used in the present invention. The Office Action acknowledged, however, that Geistlich '278 "does not teach using BioGide® to form a nerve regeneration tube for connecting nerve ends or methods of using such." (Emphasis added). The Office Action stated that Stensaas teaches methods of forming tubes for nerve regeneration, but acknowledged that "Stensaas does not teach a nerve regeneration tube for connecting nerve ends having an inner diameter of about 0.5-5mm and a length of about 10-100mm formed from a single collagen sheet of the '278 patent, or a filling material comprised of a mixture of Type I and Type IV collagen, or collagen fibers having a substantially longitudinal orientation with respect to said tube, or a filling material including laminin as a nerve growth stimulant." The Office Action further stated that Shimizu discloses a nerve regeneration tube and methods of using such comprising at least three sheets of collagen (column 6, line 48 to column 7, line 50), but which is also about 1-8mm in inner diameter with a length of about 28-35mm, but can differ according to the length of the severed portion of the nerve and thickness of the nerve. The Office Action asserted that Shimizu also teaches filling materials for a nerve regeneration tube comprising laminin and Type IV collagen and collagen Type I solution or fibers having a substantially longitudinal orientation with respect to said tube. On the basis of the above, the Office Action concluded that it would have been obvious to one of ordinary skill in the art at the time of the invention to use the single sheet collagen material of the '278 patent (BioGide®) with the teachings of Stensaas to make tubing out of said single sheet collagen material for nerve regeneration, because Shimizu teaches the advantages of a collagen nerve regeneration tube with one side smooth that inhibits cell permeation, the other side fibrous to promote biological regrowth. The Office Action stated that furthermore, a

simpler nerve regeneration tube can be produced that uses less material (single sheets of collagen as taught by Shimizu), is quicker and easier to produce, and would have the further advantage of economic savings due to lowered costs of production by reducing the need for at least three sheets of collagen to a single sheet of collagen. The Office Action further asserted that the advantageous characteristics of the two-sided collagen material of the '278 patent would suggest to and motivate the ordinary artisan to fashion the collagen material into a tube with a smooth outside and a fibrous inside in order to promote axonal regeneration in the interior of the tube as (allegedly) indicated by Shimizu. The Office Action further asserted that "even Stensaas (column 9, lines 60-67 describes the desirability of a neural regeneration tube with a smooth exterior and a rough interior."

The Office Action also stated that Applicants' previous arguments and evidence were not persuasive, essentially because they are, according to the Office Action, directed to making a neural regeneration tube as described by Shimizu, whereas the rejection is drawn to the use of a single collagen sheet material (as in Geistlich '278), by forming the sheet into a neural regeneration tube as allegedly taught by Stensaas, and not Shimizu. Furthermore, the Office Action asserted that Applicants' arguments presented in the May 21, 2008 response are similarly unpersuasive for essentially the same reasons. In that regard, the Examiner stated that

> Because the single collagen sheet material of the '278 patent already possesses a smooth and a fibrous side, the fabrication procedures of Shimizu are not required nor are they used in the formulation of the rejection. The rejection of record does NOT involve a 3-layer collagen tube; only a single sheet of Bio-Gide® formed into a tube with the fibrous collagen on the inside of said tube. Therefore, there are no unexpected results because the rejection of record does not involve a tube with a smooth interior. Applicant is attempting to set up a strawman argument by comparing the instant obvious invention to a tube with smooth interior walls and then asserting unexpected results. Unfortunately, that is NOT the grounds of the rejections of record. (Underlining in original).

The Office Action's rationale for the second rejection, noted above, including a reply to Applicant's prior remarks, is set forth at pages 6-7. The rationale is consistent with the above-cited comments with respect to the Geistlich, Stensaas, and Shimizu references. The rationale also reiterated the Office Action's earlier position regarding the asserted relevance of the Humes patent. In that regard, the Office Action stated that Humes is drawn to Type I and Type IV collagen, "in a biological context . . . with the only difference being that Humes is concerned with growing kidney cells and the instant application is drawn to growing nerves." The Office Action further asserted that "collagen is known in the art as a[n] extracellular substrate for the growth of a variety of biological cells, so it is the examiner's position that Humes is indeed analogous, pertinent, and relevant."

In response, Applicants respectfully traverse the above obviousness rejections. The present claims are directed to a nerve regeneration tube for reconnecting nerve ends, a method for producing such a tube, and a method of reconnecting nerve ends utilizing such a tube. The tube is resorbable and has a resorbable sidewall formed with collagen sheet material having a compact smooth outer barrier surface, and a soft fibrous inner surface opposite the smooth barrier surface. The tube has a compact smooth outer barrier surface formed with the compact smooth outer barrier surface of the collagen sheet material so as to inhibit cell adhesion thereon and to act as a barrier to prevent passage of cells therethrough. The tube further has a soft fibrous inner surface for promoting nerve growth, the soft fibrous inner surface of the tube being formed with the soft fibrous inner surface of the collagen sheet material. The tube has an inner diameter of about 0.5 – 5 mm, and has opposite tube ends, within which tube ends, during use, are nerve ends for reconnection of

the nerve ends, wherein the nerve regeneration tube avoids formation of scar tissue which impairs nerve healing.

In traversing the rejection, Applicants again direct attention to the Rule 132 Declaration of Dr. Myron Spector and the accompanying remarks presented in the response filed October 22, 2007, and further reiterate the comments presented in the paper filed May 21, 2008. Applicants maintain that the Declaration does indeed provide evidence of unexpected results over the prior art.

Specifically, as indicated in Dr. Spector's Declaration, the surface configuration of tubes defined by the present claims provides such tubes with unexpected properties which could not have been predicted based upon the prior art. As indicated in Applicants' previous responses, early studies (reported in exhibits B and C of the Declaration) showed that silicone nerve regeneration tubes resulted in substantially greater build-up of fibrous scar tissue within the tubes, as compared to the collagen tubes referred to in the Declaration and data. As explained previously, the problem with such fibrous build-up is that this fibrous tissue contains contractile fibroblasts (myofibroblasts) which cause the contracture of the fibrous layer. The contracting fibrous cuff interferes with the elongation of axons through the tube, and thus interferes with nerve regeneration.

As Dr. Spector's Declaration makes clear, taking into consideration the differences in the tube structure alone (between the Group V and Group IV animals), persons of ordinary skill in the art could not have predicted that the presently claimed invention, utilizing the collagen membrane material of Geistlich et al. U.S. Patent No. 5,837,278 (Group V), could result in the unexpectedly highest number of center nerve axons among the test animals, as compared to collagen tubes without a soft fibrous inner surface (the Group IV tubes).

Applicants highlighted these results in the context of comparing them to the Shimizu reference, an approach with which the Office Action has taken issue, going so far as to refer to it as a "strawman" argument. Applicants disagree with this characterization.

To reiterate, Applicants noted the following with respect to the teachings of Shimizu. The Shimizu patent discloses 3-layer tubes which have smooth collagen or gelatin inner surfaces. Shimizu discloses from column 6, line 48 to column 7, line 50 thereof, formation of a 3-layer collagen tube. A central collagen layer 21 initially is formed on a Teflon rod. This central collagen layer 21 is compressed into a high density, fine fibrous collagen layer, which necessarily and inherently imparts layer 21 with a smooth interior surface, according to Dr. Spector. After compression, the central layer 21 is removed from the Teflon rod, and the central layer 21 is repeatedly dipped into a hydrochloric acid solution containing collagen, to deposit collagen hydrochloric acid solution layers 22 and 23 on the inner and outer surfaces of the compressed collagen layer 21. According to Dr. Spector, the repeated dipping and drying procedure into collagen hydrochloric acid solution necessarily and inherently forms smooth amorphous inner and outer surface layers 22 and 23 on the compressed central layer 21 of the tube. The same result will necessarily and inherently be obtained if gelatin instead of collagen is utilized for the inner and outer surface layers. Under no conditions disclosed in Shimizu will a soft fibrous inner surface be formed.

As indicated in Dr. Spector's Declaration, based on Dr. Spector's studies and experience, the smooth inner surface that will be produced according to the methods of Shimizu will promote formation of a thick layer of fibrous scar tissue on the inner smooth surface of the tube, containing

contractile fibroblasts (myofibroblasts) which cause contracture of the fibrous layer and interference with nerve regeneration.

Notwithstanding the above evidence, the Office Action asserted that Dr. Spector's Declaration does not provide "unexpected results," because, according to the Office Action, neither the Shimizu surface topography nor Shimizu's formation of a tube are being used in the rejection. Rather, the rejection is said to rely on Stensaas for such features. Applicants maintain that in either event, the Office Action's conclusions are unfounded.

Applicants note again that the present claims refer to a soft fibrous inner surface opposite the compact smooth outer barrier surface to facilitate nerve regeneration, and that these claim features are not taught or suggested by the applied art. Stensaas refers to formation of a nerve prosthesis made of a resilient material "impermeable to fluids associated with nerve tissue." (Column 7, lines 26-28). Such materials do not include the collagen material of the present claims. In fact, the materials utilized by Stensaas are silicone rubber, polyurethane, teflon, and nitrocellulose (column 7, lines 37-39), since the reference specifically states that "it is very important that nerve prosthesis 10 be fabricated of a material which is substantially impermeable to fluids associated with nerve tissue." (Column 7, lines 52-55). Because Stensaas only utilizes synthetic, fluid-impermeable materials, persons of ordinary skill in the art would not consider utilizing its teachings for producing a nerve regeneration tube using a sheet of collagen material. Stensaas also discloses "that the outer surface of the prosthesis is smooth, while the inner surface of the prosthesis is somewhat rough or textured. The smooth outer face allows the prosthesis to slip with respect to the adjacent connective tissue, and the rough inner surface of the prosthesis provides for better adherence of the prosthesis to the nerve ends after the prosthesis is positioned." (Column 9, lines 60-67). Thus, the Stensaas

reference refers to a smooth outer face, but which is for the purpose of easy slipping of the prosthesis and not to prevent passage of cells therethrough. The very fact that the prosthesis is made of silicon rubber prevents passage of cells therethrough. Moreover, and perhaps even more pertinent to the Office Action's position, the Stensaas reference discloses a rough or textured inner surface (as specifically noted in the Office Action) for adherence to the nerve ends, while the present application provides a soft fibrous inner surface to facilitate nerve regeneration. The rough or textured inner surface of Stensaas is not the soft fibrous inner surface of the present invention. Thus, it is not clear why the Office Action insists that Shimizu is any more inappropriate for comparison than is Stensaas.

Furthermore, Applicants remind the Office that, as stated in MPEP 716.02(e), "applicant is not required to compare the claimed invention with subject matter that does not exist in the prior art" and that it is improper to require applicant to compare the claimed invention to that suggested by a combination of references, as such an approach "would be requiring comparison of the results of the invention with the results of the invention."

In that regard, Applicants maintain that the increase in nerve regeneration achieved by the present invention could not have been expected as compared with any of the cited references. Of the cited references, only Shimizu and Stensaas even refer to tubes and, as demonstrated, Applicants' invention achieves nerve regeneration that could not have been expected with the tubes of either of these references. Geistlich, of course, refers to sheet material, but makes no mention of tube formation or nerve regeneration. Thus, a nerve regeneration tube formed of the BioGide® material is not in the prior art of record (rather it is a result of a combination suggested by the Office) and thus comparison with such a tube is not appropriate. In light of the above, therefore,

Applicants maintain that the evidence presented previously does indeed show that the present invention achieves unexpected results over the prior art (regardless of which cited reference the Office Action chooses to emphasize). Accordingly, for at least this reason, the present claims are not rendered obvious by such art.

Even in the absence of the unexpected results provided, Applicants further maintain that one of ordinary skill in the art would not have selected for combination the reference teachings in the manner in which the Office Action has done so. Moreover, even if such a combination were made, the present invention would not have resulted. As Applicants have noted, one of ordinary skill in the art would not have contemplated taking the collagen single sheet material of Geistlich (for use in bone regeneration around the root of a tooth) and forming it into a nerve regeneration tube for reconnecting nerve ends, without having the Applicants' present application as a guide for doing so. Geistlich '278 contains no suggestion whatsoever of a nerve regeneration tube for reconnecting nerve ends, and no suggestion it would have been useful as such.

Shimizu discloses an artificial tube for nerve regeneration which always is formed of at least three sheets.

Stensaas et al. discloses a prosthesis for nerve regeneration which is made of a fluid-impermeable layer composed of silicone, rubber, polyurethane, teflon or nitrocellulose.

No combination of the above references suggests the invention as presently claimed. In fact, as previously noted, the prior art as a whole leads away from the present invention.

Shimizu, for example, was aware of prior use of collagen tubes for nerve regeneration, and of the problems previously associated therewith.

Persons of ordinary skill in the art, looking at all of the teachings of the prior art, would not have expected the membrane disclosed in Geistlich '278 to work as a nerve regeneration tube as presently claimed, because the prior art itself casts doubt on the efficacy of utilizing collagen tubes for nerve regeneration. This is made clear in the Shimizu reference, which states:

> Although artificial tubes for nerve which comprise collagen tubes in which collagen fibers on which laminin and fibronectin are coated are filled (Tong, X., et al., Brain Research 663: 155-162 (1994)) have recently been attempted, since the collagen tubes are unable to remain without being broken down until the nerve is regenerated to an adequate length, satisfactory results have not been obtained. (Column 1, last full paragraph).

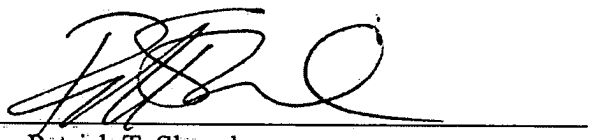
In view of the above, persons of ordinary skill in the art, taking into consideration all of the teachings of the prior art, could not have predicted the efficacy of utilizing the collagen sheet material (the Geistlich '278 membrane) for a nerve regeneration tube. Instead, because of the prior art problems associated with collagen tubes as reported in Shimizu, persons of ordinary skill in the art would not have expected the single sheet collagen tube of the present invention to work, but instead would have expected the necessity of utilizing multiple layers, as in Shimizu. For at least these additional reasons, therefore, the invention as claimed is not rendered obvious by any combination of the cited art.

Finally, as also previously noted, the Humes reference cited in the Office Action cannot be combined with Geistlich, Shimizu, and Stensaas to render the present claims obvious. Humes does not even relate to nerve regeneration tubes, but instead is directed toward a renal tubule tissue system wherein adult kidney cells are cultured in a medium which may contain Type I collagen and/or Type IV collagen. Notwithstanding that these are both within a "biological context," culturing kidney cells in a medium containing collagen offers nothing to suggest the nerve regeneration achieved by the present invention. Humes cannot be combined with the other applied

references to render obvious, or make predictable, the presently claimed invention. Therefore, for at least the reasons reiterated above, the invention is not obvious over the combination of reference teachings suggested in the Office Action. Accordingly, for at least the reasons presented above, Applicants respectfully submit that the Office Action's rejections of the claims under 35 U.S.C. §103 are improper and should be withdrawn.

Applicants believe that the present Communication fully addresses the concerns as set forth in the October 9, 2008 Office Action and that the application is in condition for allowance. Reconsideration of the instant application and an early notice of allowance are therefore requested. The Examiner is invited to telephone the undersigned if it will expedite allowance of the application.

Respectfully submitted,

By 

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